

ORIGINAL ARTICLES

Scientific and General

LYMPHOCYTIC HYPERPLASIA AND "SPONTANEOUS" ALIMENTARY LESIONS*

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IN connection with his description of lymphocytic nodules,[†] Gerlach, 1854, represented "a solitary gland" of Peyer from the colon devoid of villi and covered by very low epithelium, as shown here in Figure 1.

While studying the lingual tonsil in 1882, Stöhr found the squamous epithelium "rarefied" wherever lymphatic nodules were numerous, and observed that the surface of the epithelium was covered by large masses of clumped "lymphoid cells." He said he had thought at first that these phenomena were pathological, but convinced himself to the contrary by examining similar material from freshly decapitated animals in all of which "lymphoid cells" lay singly and in masses between the epithelial cells.

In 1884 Stöhr observed what he called a massive penetration (*massenhafte Durchwanderung*) of the squamous epithelium over lingual and faucial tonsils, constantly present, and far from pathological. He further emphasized that although the "leukocytes"‡ passed between the epithelial cells they undoubtedly not only affected the function of the latter by their mass migration, but also destroyed them. He accompanied his discussion by fine drawings, one of which (Figure 14, Plate X) is reproduced here as Figure 2. Stöhr especially considered the gaps thus formed in the epithelium and suggested that microorganisms could, no doubt, get in as well as "leukocytes" could get out.

In 1889, he also observed "leukocytes" between and within the epithelial cells over intestinal lymph nodules and hence felt compelled to admit an invasion of the epithelial cells by "leukocytes." Although Stöhr did not recognize it, his description of these epithelial cells suggests that this invasion was taking place only into degenerate cells.

When studying the human appendix, Rüdinger, 1891, said that the epithelium was invaded by lymphocytes, especially where a "ripe" lymphatic nodule approached its undersurface. He thought that this invasion is periodic and concluded that the resultant changes in the epithelium led to the formation of new lymphocytes. He also reported that whenever a lymphatic nodule became large, it

extended beyond the boundary of the muscularis mucosae and between Lieberkühn's glands (intestinal crypts) which were pushed aside, and hence took a slanting position to the follicle. He was surprised by the absence of glands over the nodules, observed degenerative changes in glands which had become surrounded by lymphocytes and emphasized that they do not disappear merely because they are pushed aside, but, like Davidoff, 1887, concluded that "leukocytes" arise from dying epithelial cells.

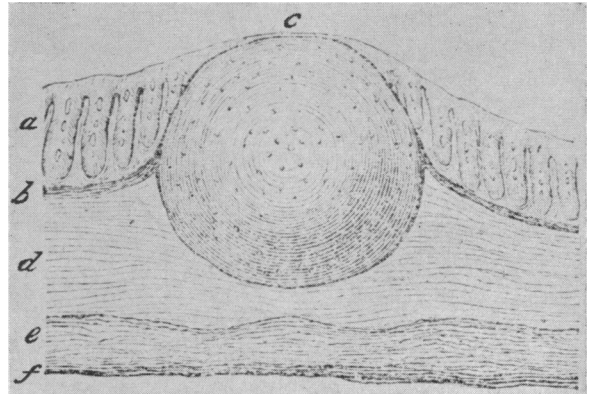


Fig. 1.—A solitary lymph nodule from the human colon after Gerlach, 1854; figure 156, showing the presence of low epithelium over the nodule. a. Lieberkühn's glands; b. muscularis mucosae; c. solitary lymph nodule; d. submucosa; e. muscularis; f. serosa X35.

It is especially noteworthy that when studying the development of the lymphatic nodules of the intestine, and the degeneration of the glands, Stöhr, 1898, found low epithelium over an appendicular nodule from a six-month-old fetus, and represented a dilated capillary very close to the undersurface of the epithelium, as represented in Figure 3.

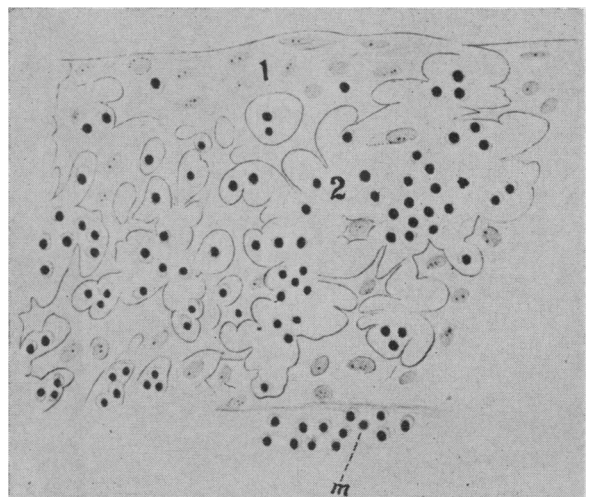


Fig. 2.—An exactly vertical section through the epithelium of a "follicular gland" from the tongue of a healthy adult male. Circa X400. The left half containing smaller and the right larger gaps in the mucosa. After Stöhr, 1884. 1. squamous surface epithelium. 2. spaces in the same made by the "leukocytes"; m. "leukocytes."

* From the Department of Anatomy, Stanford University.

† The name *Balgdrüse*—follicular gland—was given lymphatic nodules of the tongue through a misconception and unfortunately was retained in the B. N. A. in the form of lymph follicle. They are, to be sure, not follicles (bags), but nodules, and not lymphoid (lymph-like), or composed of lymph, but of lymphocytes.

‡ Stöhr chose the word *leukocytes* in preference to lymphoid cells used in his earlier publication, because he regarded it as more noncommittal.

Von Ebner, 1899, also mentioned the absence of "glands" (crypts) over aggregate nodules and

represented the epithelium without goblet cells and lower over them, in a drawing of a section taken from an appendix from a 23-year-old, beheaded individual, as represented here in Figure 4. He also represented a lymphatic nodule from the colon as having penetrated the muscularis mucosae and displaced Lieberkühn's glands, as represented in Figure 5. He found the squamous epithelium over the lymph nodules of the tongue displaced completely by leukocytes in some areas, as represented in Figure 6. A similar figure is found in the second, if not also in the first edition of the textbook of histology by Böhm and Davidoff, 1901,* and in the atlas of Sobotta, 1902 (Figure 2, Table 31). The latter found the epithelium lining a faucial, tonsillar crypt from an executed person 22 years old, in the condition represented here in Figure 7. In the legend, Sobotta stated that the basal limit of the epithelium cannot be recognized on the right, in the section, and in the second edition of this work, 1911, he again spoke of a mass passage (*massenhafte Durchwanderung*) of leukocytes through the epithelium. Since the Germans use the word "Einwanderung" for infiltration, it is clear that Sobotta, as Stöhr, 1884, who first used the term "Durchwanderung" in this connection, thought that great masses of leukocytes actually passed to the exterior through the epithelium, not merely into it.

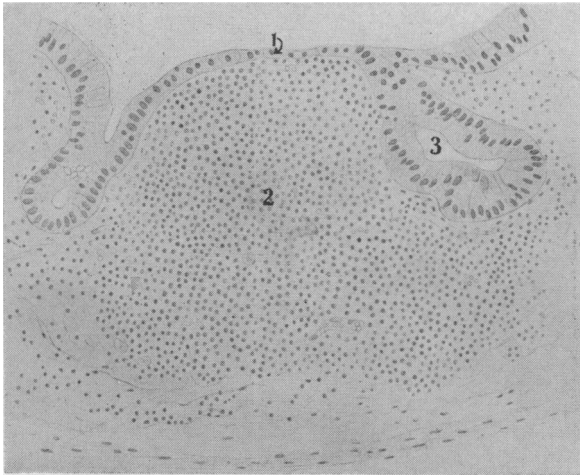


Fig. 3.—A section through an appendicular lymph nodule from a six months' fetus after Stöhr, 1898; figure 23, also showing a lower epithelium over the developing follicle. 1. epithelium; 2. lymph nodule; 3. glands of Lieberkühn; muscularis mucosae below.

AUTHOR'S OBSERVATIONS

While searching for an explanation for the very common presence of individual and multiple cysts in the pharyngeal and their practical absence in the faucial tonsils, in dissecting-room bodies, I could not help but be impressed by the striking transitions in the squamous epithelium over the surface of faucial and pharyngeal tonsils, and in their crypts, as represented in Figure 8, after Braus, 1924 (Figure 69). It will be noted that a rather sudden

transition from the usual thick squamous epithelium to a mere line containing an occasional small, degenerate nucleus, is shown on the upper right, opposite, or over, a hyperplastic lymphatic nodule. Such transitions in the epithelium were common upon the surfaces as well as in the crypts of young, decidedly hyperplastic, healthy, faucial and pharyngeal tonsils removed operatively in 1928, and fixed immediately in Bouin. It is interesting, startling, in fact, that Braus regarded the resultant lymphocytic squamous epithelial mass as a "mixed lympho-epithelial organ" in which the two cell types were in symbiosis!

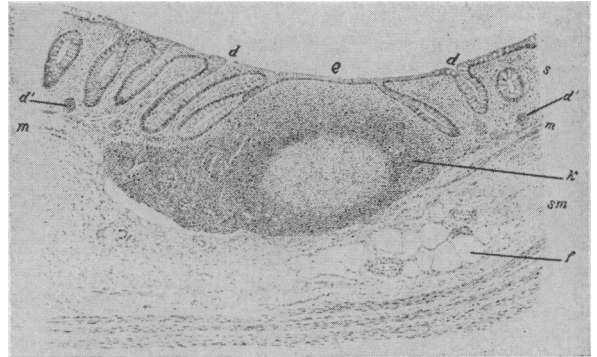


Fig. 4.—A portion of a transverse section through an appendicular lymph nodule from a 23-year-old guillotined man after von Ebner, 1899, figure 998, showing displacement of the adjacent crypts, absence of a propria, etc., and lower epithelium over the nodule. d. glands with goblet cells; d1. sections of the ends of glands; e. epithelium over the solitary nodule without goblet cells. s. mucosa. m. muscularis mucosae interrupted by the nodule; sm. submucosa with vesicles and fat cells.

Böhm and Davidoff, 1901, on the other hand, said (page 225) that "The epithelial walls of the follicular cavities often show extensive degenerative changes, which are accompanied by increased migration of leukocytes into the oral cavity," and added on the next page, "The epithelium lining the crypts or cavities of the tonsils shows, as in the lingual follicles, extensive degenerative changes, resulting mainly in the formation of variously shaped (sic), communicating spaces filled with

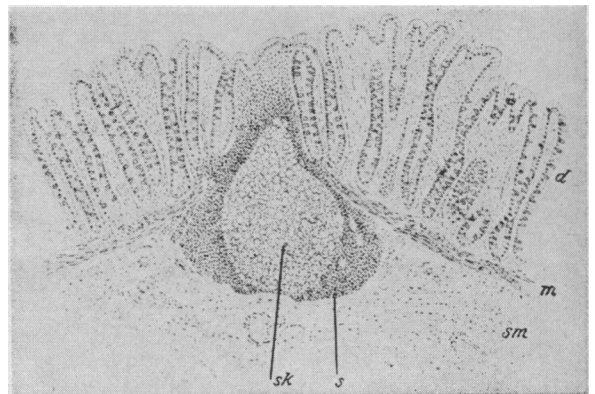


Fig. 5.—A transverse section of the colonic mucosa after von Ebner, 1899, figure 999, showing the absence of goblet cells in the epithelium over the nodule, penetration of the muscularis mucosae and extension of the lymphatic tissue to the under surface of the epithelium X35. d. Lieberkühn's gland, goblet cells dark; m. muscularis mucosae; s. solitary nodule; sk. secondary nodule; sm. submucosa.

* The first edition, in German, appeared in 1895; the second in 1898.

lymphocytes and leukocytes." Stöhr, 1884, on the other hand, thought that the infiltrated lymphocytes multiplied by mitosis, and were increased in number by further infiltration to form the spaces in the epithelium he saw and represented as shown here in Figure 2.

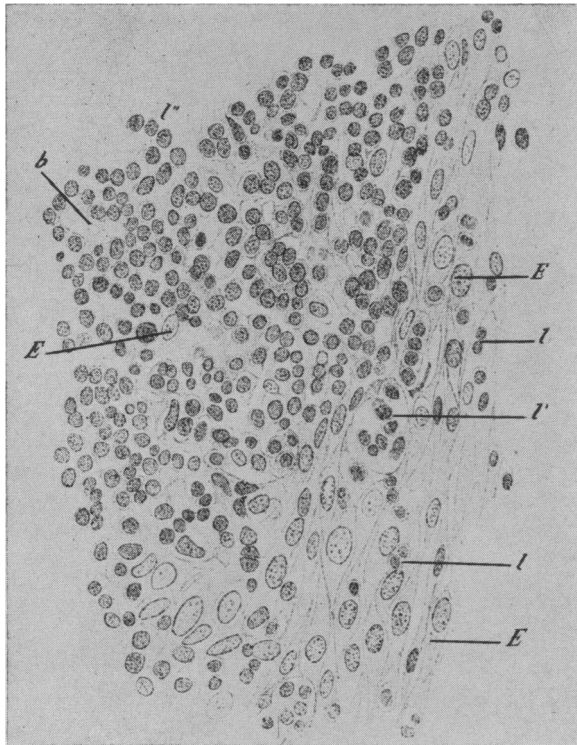


Fig. 6.—A portion of a vertical section of the epithelium from the "root" of the tongue after von Ebner, 1899, figure 898 (X500) said to show "passage" of lymphocytes through the epithelium. E=epithelium; 1, 1' and 1''="leukocytes" which in the case of 1'' have completely pushed aside (verdrängt) the epithelium; b. blood vessel.

Upon further study of lymphocytic nodules of the oral cavity and the alimentary tract, I found that similar infiltration and destruction of the epithelium occurred wherever hyperplastic lymph nodules, whether isolated or aggregate, were present and that this phenomenon was especially common and probably universal in appendices not known to be or regarded as diseased. This condition, destruction of epithelium, is illustrated well by specimens in histological teaching collections and is represented in a fine drawing by Ruth Huntington, published by Kelly, 1905, of a section from an allegedly "normal appendix," a portion of which is reproduced here as Figure 9. That similar conditions are common in appendices is indicated by the studies of Aschoff, 1912 and 1930, and especially by that of Shelly, 1937, of 155 and 2,065 appendices, respectively, removed incidentally.

The absence of villi, crypts and goblet cells especially over aggregate lymph nodules has long been known, and that the last two also may disappear over hyperplastic lymphatic nodules in the appendix also was noted. Unless the crypts remained intact and gradually shortened until they disappeared, it follows that their destruction accompanying

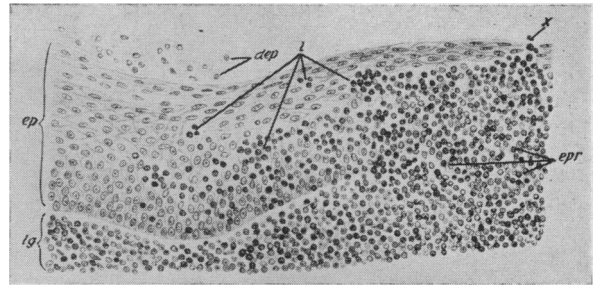


Fig. 7.—A section through a part of the mucosa of a tonsillar sulcus (Bucht) (crypt) after Sobotta, 1902, figure 2, plate 31, said to illustrate the penetration (Durchwanderung) of the epithelium by "leukocytes" until only nests of epithelial cells are left at the right where the basal limits of the epithelium are said to be unrecognizable. (X220.) d. ep., desquamated epithelium in a tonsillar sulcus; ep., epithelium; ep. r., epithelial remnants; l, leukocytes; lg, lymphoid tissue of the mucosa; X, leukocytes advancing into lumen of a tonsillar crypt.

lymphatic hyperplasia must be accompanied by the production of a break, or breaks, in continuity somewhere along their tubular bodies. Moreover, marked lymphatic hyperplasia cannot occur without derangement of the architecture of the mucosa and interference with the function of the structures affected.

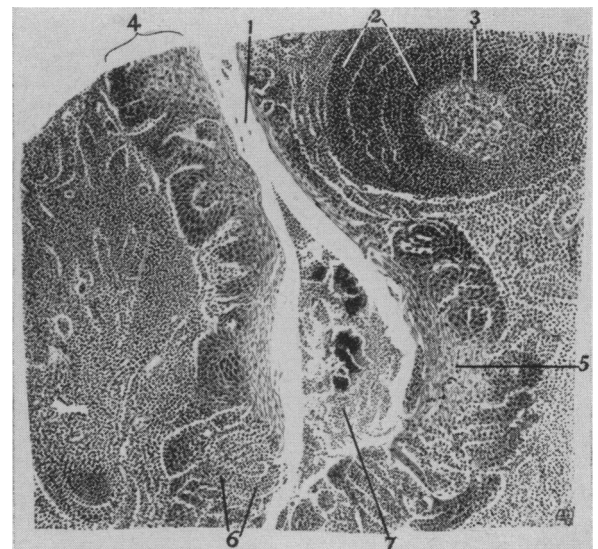


Fig. 8.—Migration of lymphocytes into epithelium of a crypt. (X68.) After Braus, 1924. Note especially the region of the nodule where the epithelium is reduced to a very thin layer containing a few degenerate nuclei. 1. individual desquamated epithelial cells; 2. cortex of the lymph follicle. 3. germ center; 4. epithelium; 5. epithelium containing few lymphocytes; 6. intense infiltration with lymphocytes; 7. desquamated "epithelia" and emigrated lymphocytes in the interior of the tonsillar sulcus (crypt).

Bauer, 1921 (page 448), called attention to the relation between anatomical and functional disturbances in the intestinal absorption areas associated with "inordinate loading" with albumen alone, which resulted in the entrance of foreign protein. How much greater, then, may such absorption become when epithelium—squamous or columnar—is decidedly atrophic or destroyed altogether! Moreover, upon the exposure of the hyperplastic lymphatic tissue to the lumen, external agents of all kinds can freely enter or attack it. Because of the

great number of lymphatic nodules in the alimentary canal, an endless number of places of lowered resistance of all degrees hence can be formed through, or during, lymphatic hyperplasia alone. It is not necessary, to be sure, that more than one nodule becomes hyperplastic to intensify the allergic response or permit infection. The occurrence of local responses of lymphatic tissue are well established and that places of damage to the epithelium commonly are present in the alimentary tracts from individuals devoid of clinical signs or symptoms of disease, has been abundantly established through microscopic examination. However, it is not implied, to be sure, that loci of lower resistance are not produced in any other way or that their production must always be accompanied by lymphatic hyperplasia, infection or clinical symptoms or signs of illness.

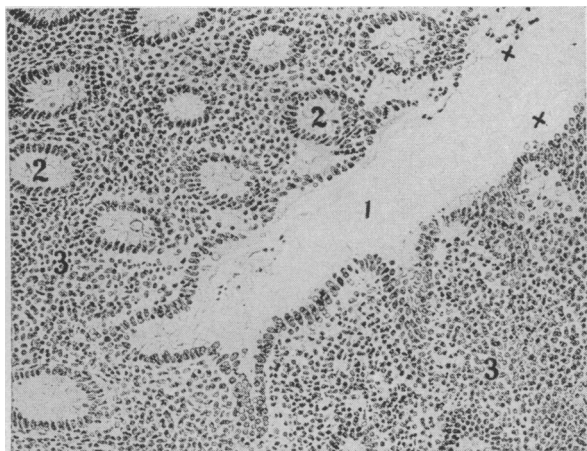


Fig. 9.—“Portion of the normal mucous membrane of appendix X150” from Kelly, 1905.—Note the absence of epithelium at X along the upper portions of the appendicular sulcus. Only the pertinent portion of the original is reproduced here. 1. sulcus in the appendicular mucosa; 2. crypts in section; 3. lymphocytes.

The atrophy and destruction of squamous and columnar epithelium of the alimentary tract emphasized here, and the related phenomena, it seems to me, offer a satisfactory answer to Aschoff's question, 1912 (page 99), as to “why the harmless residents of the appendix suddenly cause an acute attack” and confirm his conclusion, reached after a generation of study, that “The condition for the occurrence of appendicitis must reside in the normal appendix and its pathogenesis can only be studied with success on such pure cases.” They further explain why “Appendicitis arises purely locally as a rule in the distal portion of the appendix” and why (page 16) “Every case of appendicitis develops on the basis of a local enterogenous infection in a specifically disposed appendix.” Although not every case arises in this way, this does not invalidate my conclusion.

My observations do not confirm his belief that the cause of appendicitis “must and will be found in mechanical conditions” such as a slight flexure of the distal portion of the appendix, stressed by Aschoff. However, in so far as such very slight and severer flexures are due to asymmetrical lymphatic

hyperplasia, so common not only in the appendix, or to consequent local obstruction of its lumen, mechanical conditions may, to be sure, be involved.

Furthermore, Aschoff (page 5) probably was correct in saying that “in the majority of cases, in which especially marked development of the lymph nodules, a very marked increase of the lymphatic elements . . . is present, we must think of a local or general status lymphaticus.” It is of special interest that Shiota, 1909, concluded that there was a direct relationship between lymphatism and the length of the appendix and that Bauer, 1921, felt that a constitutional factor was concerned in appendicitis.

Aschoff, 1911 (page 759), claimed that in cases of acute appendicitis, six hours after the onset of symptoms of abdominal and localized pain on pressure and low fever, the “primary infect”^{*} can always be found upon microscopical examination of the appendix, even when it looks entirely normal except for slight injection of the serosa. He emphasized that a sufficiently careful microscopic search always reveals a slight epithelial defect in one of the sulci in the mucosa, which contains a plug composed of leukocytes and fibrin from which a marked, wedge-shaped mass of “leukocytes” penetrates all layers of the appendicular wall, even when the serosa showed only slight evidences of beginning exudation. It is difficult to believe that the defect which Aschoff called the “Primarinfekt” actually was not a locus minoris resistentiae in the epithelium produced by lymphatic hyperplasia instead of such a manifest artifact as he represented, or that the cases of fleeting or fugitive appendicitis, of which he and others have spoken, are not occasioned by periodic hyperplasia in lymphatic nodules with the production of primary defects in the mucosa sufficient to produce disease.

DISCUSSION

The best-known characteristics of lymphatic tissue are its extraordinary variability in number, size and state, and its great lability. Passow, 1885, emphasized this in regard to the number of the intestinal nodules in different individuals, and Hofmeister, 1887, observed regressive changes in “adenoid tissue” in starvation. Stöhr, 1889, concluded that three days of starvation had greatly reduced the size of the nodules, and the withholding of food in cases of acute appendicitis, gastric and duodenal ulcers has become well established in practice. Aschoff referred to the reported infrequency of appendicitis during starvation in Russia, and the effect of diet upon lymphatic tissue was shown more recently by Settles (1920), Lefholz (1923), and Jackson (1925).

The reaction of the lymphatic nodes to physiological states such as exercise, pregnancy, etc., also

^{*} The drawing (Fig. 19, Pl. IV, Aschoff, 1908) of a “Primarinfekt” is highly impeachable evidence, however. Such “Infekte” are present in large numbers in routine material. What is greatly needed is complete series of sections of entire appendices from persons of different ages not known to have suffered from appendicitis.

is well established and they may be allergic to various inhaled as well as ingested substances. Such allergic reactions could explain recurrent light or severe attacks not only of tonsillitis and appendicitis, but of ulcer—especially of esophageal, gastric, or duodenal ulcers. The occurrence of such loci of lowered resistance, and even of open portals in the mucosa, also can account for the common presence of relatively large masses of lymphocytes in apparently normal appendices, and over tonsils, which merely are hyperplastic. Were these masses to be regarded as having been formed through individual migration through a normal mucosa that migration would have to be far more active and the lymphocytes far more resistant than known to be after their entrance into the alimentary tract.

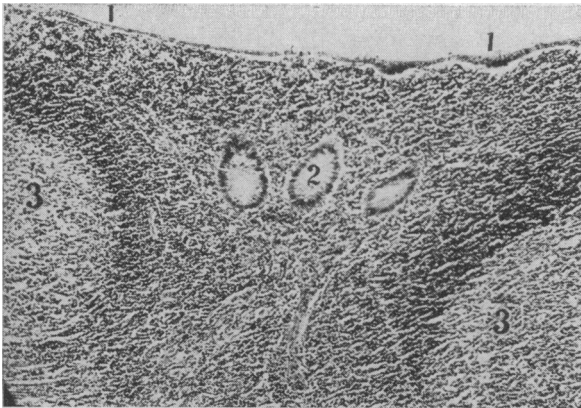


Fig. 10.—A photograph of a small portion of a transverse section of an appendix from a 32-year-old man (X75) showing the effect of lymphatic hyperplasia upon the epithelium and mucosa. 1. greatly reduced epithelium; 2. sections of a few remaining crypts; 3. lymph nodules. All the rest of the field is occupied by lymphocytes; no propria remaining. From the collection of Professor Alvin J. Cox.

The destruction of the appendicular epithelium and mucosa,* in consequence of noninfectious processes, offers a satisfactory explanation for the normal, nonpathogenic obliteration of the appendix, and can explain why that obliteration usually begins distally and why local constrictions and obliteration often occur. The lymphatic hyperplasia also offers an explanation for the so-called "erected" appendices which seem normal, and for temporary or periodic occlusions of the lumen or light passing attacks of appendicitis and for so-called "spontaneous" ulcer here and elsewhere in the alimentary tract.

That the atrophy and destruction of the tonsillar, appendicular, etc., epithelium—and mucosa—is effected from below and not from the surface, is splendidly illustrated by such specimens as represented in Figure 10. In this cross-section of an appendix from a 32-year-old male, only remnants of crypts, muscularis mucosae and epithelium remain over its entire interior. Wherever hyperplastic nodules approached near to the lumen, only

an extremely thin remnant of the epithelium is left and contains some small gaps through which lymphocytes and blood have entered the lumen which contains some fecal contents. Aschoff, 1908, emphasized that he always found the appendicular mucosa intact over concretions, and the evidence that the alimentary mucosa suffers change from below in loci of lymphatic hyperplasia is conclusive. The main factors in this process seem to be interference with nutrition and lysis, not phagocytosis or disease as commonly understood. That even slight bleeding where defects exist may also facilitate infection needs no comment.

I realize, to be sure, that the constant association of phenomena does not in itself relate them as cause and effect. However, since the existence of loci of lowered resistance of all degrees from the disappearance of brush borders and goblet cells to complete destruction of the mucosa is undeniable, the manner of their production cannot affect the conclusions drawn regarding the possibility of infection through, or digestion of, damaged epithelium and destruction or sloughing of the nodules. Moreover, not only the epithelium but the entire mucosa and even portions of the submucosa may be and often are affected by the hyperplasia, including smooth muscle, etc., in the villi as well as in the muscularis mucosae. In cases of marked diffuse hyperplasia, all these structures may be involved similarly.

That the control of lymphatic hyperplasia may point the way to relief from various lesions of the alimentary tract would seem self-evident and should need no emphasis. I shall, therefore, refrain from citing manifold evidence from clinical literature in support of the conclusion presented here upon the basis of evidence revealed by others and upon personal and departmental observations and other material kindly put at my disposal by my colleague, Professor Cox.

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(References continued on page 240)

* In the older literature, the word mucosa is sometimes used in a restricted sense. It, of course, includes epithelium, propria and muscularis mucosae, with the contained vessels, nerves and lymphatic tissue.

Steps Taken to Continue California Physicians' Service In Vallejo

A most serious crisis threatens Chabot Terrace if the California Physicians' Service withdraws its activities on September 30 as planned, according to Ray Martin, 412 Siskiyou Avenue, Chabot Terrace, who was appointed chairman of the "Save the California Physicians' Service" Committee at a business meeting of the CCCC's Monday evening.

Mr. Martin pointed out the obvious hazard to the community in case of epidemics in the face of the present shortage of nurses and doctors. He pointed out the financial record of the Chabot Medical Center as evidence that it cannot operate without a better contract. It must break even at least. In May the total income was \$13,486.15 and the total expenditures, \$19,555.76, leaving a deficit of \$6,069.61.

A plan was evolved Friday at a meeting at Harbor Gate Project in Richmond which Mr. Martin attended, calling for every housing project in the bay area to petition Washington to make it possible for the California Physicians' Service to be retained.

Thursday and Friday of this week, August 26 and 27, petitions will be circulated in Chabot Terrace. Everyone interested in the welfare of his family is asked to sign the petition and to help in its circulation. Those willing to assist are asked to see Mr. Martin or Project Services Office.—Vallejo News-Chronicle, August 25.

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(Continued from page 214)

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MEDICAL EPONYM

Stokes's Collar

William Stokes (1804-1878) first described this phenomenon in the *Dublin Journal of Medical and Chemical Sciences* (5:400-440, 1834), in an article entitled "Researches on the Diagnosis and Pathology and Aneurysm." He discusses a case of aneurysm of the aorta as follows:

"I was at once struck with the peculiar appearance of the neck. This was generally enlarged (giving the idea of the patient's wearing a collar or tippet), the jugular veins were turgid and tortuous."

He also mentions the phenomenon in the first part of *A Treatise of the Diagnosis and Treatment of Diseases of the Chest* (Dublin, 1837, page 231) and again in *The Diseases of the Heart and the Aorta* (Dublin, 1854, page 573), as follows:

"As an indication of intrathoracic tumor, an extremely varicose state of the superficial veins of the neck and thorax is probably less frequent in aneurismal than in cancerous diseases. The pressure may be exercised on the venae innominae or the superior cava. . . . In other cases we find that in place of the large tortuous veins ramifying on the surface, there is a puffy elastic swelling of the entire neck. To this may be given the name of tippet-like swelling of the neck."—R. W. B., in *New England Journal of Medicine*.